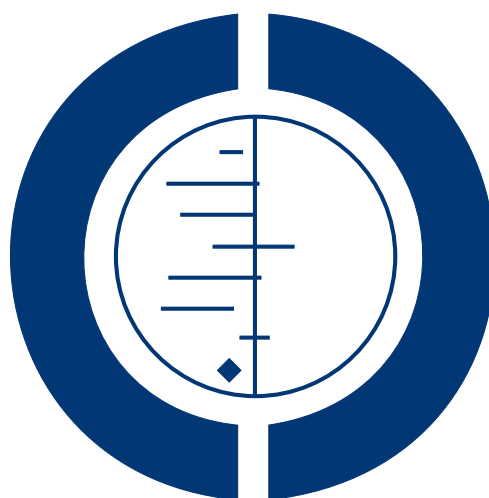


# Artesunate versus quinine for treating severe malaria (Review)

Jones KL, Donegan S, Lalloo DG



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[Intervention Review]

# Artesunate versus quinine for treating severe malaria

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## ABSTRACT

### Background

Severe malaria kills over a million people every year. We sought evidence of superiority of artesunate compared with the standard treatment quinine.

### Objectives

To compare artesunate with quinine for treating severe malaria.

### Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (July 2009), CENTRAL (*The Cochrane Library* 2009, Issue 3), MEDLINE (1966 to July 2009), EMBASE (1974 to July 2009), LILACS (1982 to July 2009), ISI Web of Science (1945 to July 2009), the *meta*Register of Controlled trials (*mRCT*), conference proceedings, and reference lists of articles. We contacted researchers and the World Health Organization.

### Selection criteria

Randomized controlled trials comparing intravenous, intramuscular, or rectal artesunate with intravenous or intramuscular quinine for treating adults and children with severe malaria who are unable to take medication by mouth.

### Data collection and analysis

Two authors assessed the eligibility and risk of bias of trials, extracted and analysed data, and drafted the review. The third author contributed to the design and writing of the review. Death was the primary outcome. Dichotomous outcomes were summarized using risk ratios (RR) and continuous outcomes by mean differences (MD). Where appropriate, we combined data in meta-analyses. Heterogeneity was investigated for the primary outcome using subgroup analyses.

### Main results

Six trials enrolling 1938 participants (1664 adults and 274 children) met our inclusion criteria. All six trials were conducted in Asia, and only one small trial enrolled only children. Five trials used intravenous artesunate and one trial intramuscular artesunate; all six used intravenous quinine. Treatment with artesunate significantly reduced the risk of death (RR 0.62, 95% CI 0.51 to 0.75; 1938 participants, 6 trials), reduced parasite clearance time (MD 8.14 h, 95% CI 11.55 to 4.73; 292 participants, 3 trials), and hypoglycaemia detected by routine monitoring (RR 0.46, 95% CI 0.25 to 0.87; 185 participants, 2 trials). There was no evidence of a difference in neurological sequelae, coma recovery time, time to hospital discharge, fever clearance time, or adverse effects other than hypoglycaemia.

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**Artesunate versus quinine for treating severe malaria (Review)**

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## Authors' conclusions

Intravenous artesunate is the drug of choice for adults with severe malaria, particularly if acquired in Asia. This review did not identify sufficient data to make firm conclusions about the treatment of children or the effectiveness of intramuscular artesunate. There is an urgent need to compare the effects of artesunate with quinine in African children with severe malaria. The applicability of these results to Asian children and the ethics of further research are points of debate.

## PLAIN LANGUAGE SUMMARY

### Artesunate reduces death from severe malaria in adults in Asia, but there is not enough evidence to say how effective artesunate is in children, people in Africa, or on potential adverse effects

Severe malaria kills over a million people every year. The annual death toll can be as high as one in a 100 children under the age of five. Severe malaria occurs when infection with the malaria parasite is complicated by serious failure of the body's major organs. Sometimes it is associated with coma (known as cerebral malaria). Following cerebral malaria a small proportion of children suffer with long-term neurological disability.

Quinine, the standard treatment for severe malaria, often causes adverse effects. In most people symptoms are mild; less common but more serious adverse effects include low blood sugar and heart rhythm disturbances. Regular glucose measurement and a heart trace are therefore advised when quinine is given by injection. Lack of resources may not permit this monitoring in some settings.

Artesunate is generally well tolerated, safe, and does not require any monitoring. Artesunate comes from a family of drugs known as the artemisinin derivatives. Another drug from this group, artemether, has shown no reduction in death compared to quinine. Artemether absorption is erratic and unreliable. By contrast, artesunate levels peak reliably and predictably within an hour.

The review of trials assessed the effectiveness of artesunate versus quinine. Six trials involving 1938 people (1664 adults and 274 children) were identified, all undertaken in Asia. Treatment with artesunate significantly reduced the risk of death. It also reduced the time taken to clear parasites from the blood and reduced the number of people with low blood sugar during follow up in trials where this was routinely measured. There was no evidence to say if the drug is effective in children in Africa, in whom most deaths from severe malaria occur.

## BACKGROUND

Severe malaria kills over a million people every year with annual death rates of up to one in a 100 children under the age of five (WHO 2000; Trape 2001). A small proportion of children may also suffer from long-term neurological disability as a consequence of severe malaria.

Severe malaria occurs when infection with the *Plasmodium falciparum* parasite is complicated by serious organ failure or metabolic abnormalities (Gilles 2000); cerebral malaria, unrousable coma not attributable to any other cause, is a specific type of severe malaria (Gilles 2000) that even with correct treatment can have a mortality rate approaching 20% (Jaffar 1997). A small proportion of survivors of cerebral malaria are left with persistent neurological sequelae. Severe malaria occurs most commonly in those with lim-

ited immunity to malaria. In highly endemic areas, young children are therefore at most risk of severe disease and death, whereas in areas of lower endemicity and travellers, both adults and children get severe disease (White 2003).

The standard treatment for severe malaria is an intravenous infusion of quinine (WHO 2000). Quinine may also be administered as an intramuscular injection. A loading dose of 20 mg/kg is recommended to reduce the time needed to reach effective concentrations in the blood (White 1982). A Cochrane Review found a significant reduction in fever clearance time and parasite clearance time with a loading dose compared with no loading dose but concluded that data were insufficient to demonstrate an impact on risk of death (Lesi 2004).

Adverse effects resulting from quinine therapy are common. Cinchonism (symptoms of quinine overdose) often occurs at conventional dose regimens. This usually mild and reversible symptom complex consists of tinnitus, deafness, dizziness, and vomiting, and may affect adherence. Hypoglycaemia is a less common but more serious adverse effect (White 1983). Some people are allergic to quinine and develop skin rashes and oedema even with small doses. Toxic levels of quinine can occur following rapid intravenous administration and can result in heart rhythm disturbances, blindness, coma, and even death (Sweetman 2005); hence the recommendation for routine cardiac monitoring during parenteral treatment (BNF 2007). In some parts of the world, such as South-East Asia, there is limited evidence of declining efficacy to quinine in severe malaria (Wongsrichanalai 2002).

Artesunate and other artemisinin derivatives offer an alternative to quinine for severe malaria. Artemisinin derivatives are produced from the leaves of the plant *Artemisia annua* and are less stage specific than quinine, killing young ring forms before sequestration has occurred (ter Kuile 1993). Drugs from this group clear malaria parasites faster than other agents, cure infections with multi-drug resistant *P. falciparum*, and reduce gametocyte carriage, and thus potentially the transmission (spread) of malaria (Adjuik 2004). In contrast to quinine, administration of artemisinins does not require cardiac monitoring and therefore may be a more practical option in resource-poor settings. Trials examining whether the artemisinin derivative artemether is more effective than quinine have not shown a reduction in mortality (AQMSG 2001). However, artemether, an oil-based intramuscular formulation, is prone to erratic and partial absorption (Karbwang 1997; Murphy 1997; Mithwani 2003). In contrast, artesunate may be given by intramuscular or intravenous injection with peak concentrations reliably achieved within one hour of administration (Nealon 2002; Hien 2004).

Artemisinins are widely reported to be safe (Sweetman 2005). Animal studies using very high doses of artemisinins have demonstrated focal brain stem lesions particularly affecting the auditory pathways (Brewer 1994; Nontprasert 1998; Genovese 2000; Nontprasert 2000; Nontprasert 2002). Many studies of brain stem function in humans, including audiometry, have failed to show any abnormality following repeated courses of artemisinins (Ribeiro 1998; Kissinger 2000). To date, only one nested case-control study has demonstrated a significant audiometric hearing loss in factory workers treated with artemether-lumefantrine for uncomplicated malaria compared with workers with no history of exposure to malaria infection or artemether-lumefantrine (Toovey 2004). This result needs to be interpreted with caution due to a number of design limitations.

A Cochrane Review prepared in year 2000 assessed the effects of the artemisinin derivatives, including artesunate, for treating severe malaria (McIntosh 2000). This review has since been superseded by a series of Cochrane Reviews examining the differ-

ent artemisinin derivatives, and our review concerns trials in artesunate for severe malaria.

## OBJECTIVES

To compare artesunate with quinine for treating severe malaria.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled trials.

#### Types of participants

Adults and children with severe malaria who are unable to take medication by mouth.

#### Types of interventions

##### Intervention

- Intravenous, intramuscular, or rectal artesunate.

##### Control

- Intravenous or intramuscular quinine.

#### Types of outcome measures

##### Primary

- Death.

##### Secondary

- Neurological sequelae.
- Coma recovery time.
- Time to hospital discharge.
- Fever clearance time.
- Parasite clearance time.

## Adverse effects

- Serious adverse effects resulting in discontinuation of treatment (eg biochemical abnormalities, cardiac effects).
- Hypoglycaemia (symptomatic or asymptomatic).
- Other adverse events, including tinnitus, hearing impairment, nausea, and vomiting.

## Search methods for identification of studies

We have attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and ongoing).

## Databases

We searched the following databases using the search terms and strategy described in [Appendix 1](#): Cochrane Infectious Diseases Group Specialized Register (July 2009); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2009, Issue 3); MEDLINE (1966 to July 2009); EMBASE (1974 to July 2009); LILACS (1982 to July 2009); and ISI Web of Science (1945 to July 2009). We also searched the *metaRegister* of Controlled trials (*mRCT*) using artesunate and quinine as search terms.

## Conference proceedings

We searched the following conference proceedings for relevant abstracts: 4<sup>th</sup> Multilateral Initiative on Malaria (MIM) Pan-African Malaria Conference, 13 to 18 November 2005, Yaoundé, Cameroon; 4<sup>th</sup> European Congress on Tropical Medicine, 11 to 15 September 2005, Marseille, France; ACT NOW. An International Symposium on Malaria, 29 to 30 April 2004, Colombia, New York, USA; 2<sup>nd</sup> International Malaria Research Conference, John Hopkins Malaria Research Institute, 25 to 26 March 2004, Maryland, USA; 3rd MIM Pan-African Conference, 18 to 22 November 2002, Arusha, Tanzania; and the 3rd European Congress on Tropical Medicine and International Health, 8 to 12 September 2002, Lisbon, Portugal.

## Researchers, organizations, and pharmaceutical companies

We contacted individual researchers working in the field and the World Health Organization for unpublished and ongoing trials in January 2006.

## Reference lists

We checked the reference lists of existing reviews and of all trials identified by the above methods.

## Data collection and analysis

### Selection of studies

All trials identified by the search strategy were screened by Katharine Jones (KJ) and Sarah Donegan (SD) and full reports of potentially relevant trials were obtained. KJ and SD independently applied the inclusion criteria to the full reports using an eligibility form and scrutinized publications to ensure each trial was included in the review only once. Trial authors were contacted for clarification if necessary. Disagreement was resolved by discussion with David Lalloo (DL).

### Data extraction and management

KJ and SD independently extracted data using a data extraction form. For each outcome we aimed to extract the number of participants randomized and the number analysed in each treatment group. For dichotomous outcomes, we recorded the number of participants experiencing the event and the number assessed in each treatment group. For continuous outcomes, we extracted arithmetic means and standard deviations for each treatment group, together with the numbers assessed in each group. If medians had been used we also extracted ranges whenever it was possible.

### Assessment of risk of bias in included studies

KJ and SD independently assessed the risk of bias in each trial and recorded the results in a table. The generation of the allocation sequence and allocation concealment were classified as adequate, inadequate, or unclear according to [Jüni 2001](#). Descriptive data were collected on whether participants, providers, and outcome assessors were blind to the treatment given. Inclusion of all randomized participants (proportion of participants included for which an efficacy endpoint is available) was classified as adequate (if > 90%), inadequate (if ≤ 90%), or unclear. Trial authors were contacted for clarification if necessary. Disagreement was resolved by discussion with the third author.

### Data synthesis

We analysed the data with [Review Manager 5](#) (RevMan) using risk ratio (RR) for dichotomous data, mean difference (MD) for continuous data, and 95% confidence intervals (CI). Medians and ranges were reported in a table. If arithmetic means were reported, normality of the data was checked by calculating the ratio of the mean over the standard deviation ([Altman 1996](#)). If this test suggested the data were skewed (ie if the ratio was less than 2), we commented on this in the text but still combined the results in a meta-analysis.

If there was discrepancy between the number randomized and the number analysed, we calculated the percentage loss to follow up for each treatment group and reported this information. Originally, we aimed to analyse data according to the intention-to-treat principle (all randomized participants should be analysed in the groups to which they were originally assigned). However, since for some trials it was unclear whether there was loss to follow up, we entered the number analysed into RevMan whenever these figures were available. By attempting to carry out a complete-case analysis in this way, we have tried to avoid making assumptions about the outcomes of participants that were lost to follow up.

We looked for statistical heterogeneity by inspecting the forest plots for overlapping confidence intervals, applying the chi-squared test (P-value < 0.10 considered statistically significant), and the  $I^2$  test ( $I^2$  value of 50% used to denote moderate levels of heterogeneity). If heterogeneity was detected but it was still considered clinically meaningful to combine studies, a random-effects model was used. The potential sources of heterogeneity explored for the primary outcome measure were prespecified in the protocol or post-hoc. The prespecified sources were allocation concealment, blinding, participant age (children versus adults), and drug regimen (loading dose versus no loading dose of quinine and use of any additional antimalarials). The post-hoc sources were presentation of severe malaria (severe versus cerebral malaria), method of diagnosing malaria (blood film versus rapid diagnostic test), route of artesunate administration (intravenous versus intramuscular), time since admission to hospital (before and after 48 hours since admission), and hyperparasitaemia.

As only one small trial used intramuscular artesunate we presented these results as a subgroup analysis rather than pooling data according to route of administration as stated in the protocol.

We constructed funnel plots to look for evidence of publication bias. The small number of trials included in the meta-analyses precluded meaningful use of these plots.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

The six trials that met our inclusion criteria enrolled a total of 1938 participants of which 1664 were adults and 274 were children. Only one trial enrolled only children (Cao 1997); this small trial included 72 children. Results for children in the other trials could not be separated out for analysis (see 'Characteristics of included studies'). We identified one ongoing study, a large multicentre trial in African children (see 'Characteristics of ongoing studies'). Thirteen trials detected by the search specifications were excluded from the review (see 'Characteristics of excluded studies').

### Location

Four trials took place in single centres in Vietnam. The other two were multicentred: Newton 2003 had two centres in Thailand; and Dondorp 2005 had 11 centres throughout Bangladesh, Myanmar, India, and Indonesia.

### Source of funding

Three trials were funded by a medical research charity, one by international organizations including the World Health Organization, and one, Anh 1989, had contributions in the form of the study drugs from pharmaceutical companies. Funding was not specified for one trial (Hien 1992).

### Participants

Anh 1989, Hien 1992, and Anh 1995 enrolled only adults with cerebral malaria; Cao 1997 included only children with cerebral malaria; Newton 2003 included only adults with severe malaria; and Dondorp 2005 included both adults and children with severe malaria. All trials except Dondorp 2005 used the presence of *P. falciparum* parasitaemia to confirm the diagnosis of malaria. Dondorp 2005 used a positive rapid diagnostic test. Although standardized clinical definitions for severe malaria exist, entry criteria were not consistent across trials.

### Interventions

All trials compared artesunate with quinine. Artesunate was given intravenously in five trials and intramuscularly in one trial (Cao 1997). Quinine was given intravenously in all six trials with an initial loading dose in four of these. Drug dosage and duration of treatment varied between the trials (see 'Characteristics of included studies' for details). Five trials gave an additional oral antimalarial to at least one of the treatment arms, which was unmatched between the treatment arms. Two trials, Hien 1992 and Cao 1997, included an additional rectal artemisinin arm that was not pertinent to this review.

### Supportive care

All six trials reported measuring blood glucose on admission, but only four trials reported any subsequent monitoring for hypoglycaemia. Three trials reported routine measurement of blood glucose at variable time intervals; monitoring of all participants several times a day (Newton 2003); monitoring of all participants every four hours for the first 24 hours and then every six hours in any participants with coma, prostration, jaundice, or more than one complication (Cao 1997); monitoring in all participants on days 1, 3, 7, and 14 (Anh 1989). Blood glucose was only measured in those participants with clinical signs of hypoglycaemia in one trial (Dondorp 2005).

### Outcome measures (defined in Appendix 2)

All six trials reported death as an outcome. Two trials reported neurological sequelae at discharge (Cao 1997; Dondorp 2005). Five trials reported coma recovery time (Anh 1989; Hien 1992; Anh 1995; Cao 1997; Newton 2003), and four trials reported fever clearance time (Hien 1992; Anh 1995; Cao 1997; Newton 2003). Reporting of parasite clearance time varied between trials and included parasite clearance times of 50%, 90%, 95%, and 100%. We chose to include data for parasite clearance time of 50% as this was most frequently reported in the trials (Anh 1989; Hien 1992; Anh 1995; Cao 1997; Newton 2003). Three trials reported time to hospital discharge (Cao 1997; Newton 2003; Dondorp 2005). Three trials reported adverse effects including hypoglycaemia (Cao 1997; Newton 2003; Dondorp 2005).

### Length of follow up

Cao 1997 specified that participants were asked to return for a follow up visit three weeks after discharge from hospital. None of the other trials reported the length of follow up.

### Risk of bias in included studies

See Table 1 for a summary of the assessment of the risk of bias in the trials. Further details are located in the 'Characteristics of included studies'.

Table 1. Risk of bias assessment

Trial	Randomization <sup>a</sup>	Concealment <sup>a</sup>	Blinding	Inclusion <sup>a</sup>
Anh 1989	Adequate	Inadequate	Open label	Unclear
Hien 1992	Adequate	Adequate	Participant blinded	Unclear
Anh 1995	Adequate	Adequate	Open label	Unclear
Cao 1997	Adequate	Adequate	Open label	Adequate (100%)
Newton 2003	Adequate	Inadequate	Open label	Adequate (100%)
Dondorp 2005	Adequate	Adequate	Open label (trial centre, microscopists assessing blood slides, and data analysts blinded until trial end)	Adequate (100%)

<sup>a</sup>Generation of allocation sequence, allocation concealment, and inclusion of all randomized participants.

The generation of the allocation sequence was adequate in all six trials. Allocation concealment was adequate in four trials; Anh 1989 and Newton 2003 reported that the randomization was open. In all six trials, investigators were aware of treatment allocation. Participants were blind to the intervention in Hien 1992, and microscopists and data analysts were blind to the intervention in Dondorp 2005. Newton 2003 and Dondorp 2005 clearly stated that no participants were lost to follow up. We were able to obtain individual patient data for one trial in which primary outcomes available for all included participants (Cao 1997). The number of participants randomized was used in the analysis for the remaining three trials (Anh 1989; Hien 1992; Anh 1995).

## Effects of interventions

### Death

Death was reported in all six trials. Treatment with artesunate significantly reduced the risk of death (RR 0.62, 95% CI 0.51 to 0.75; 1938 participants, 6 trials, Analysis 1.1) with a consistent reduction across trials. A subgroup analyses of trials reporting mortality before and after 48 hours since admission to hospital found no difference between the groups within 48 hours (1646 participants, 3 trials, Analysis 1.2).

In view of significant variation in trial design we explored potential sources of heterogeneity for mortality. We found that excluding trials with inadequate allocation concealment (Analysis 1.3), trials in which all participants had cerebral malaria (Analysis 1.4), and those with no loading dose of quinine (Analysis 1.5) did not alter the significance of the result. The one trial in which all participants were children found no evidence of a difference between the artesunate and quinine (72 participants, 1 trial, Analysis 1.6). This small trial was also the only trial to use an intramuscular formulation of artesunate (Analysis 1.7). Only one trial looked at the effect of hyperparasitaemia on death (Dondorp 2005). It found that artesunate was more effective than quinine only in those participants with hyperparasitaemia (RR 0.26, 95% CI 0.14 to 0.49; 229 participants, 1 trial), with no evidence of a difference in those participants with no hyperparasitaemia (1153 participants, 1 trial). This result needs to be interpreted with caution as these subgroups may not be truly randomized.

### Neurological sequelae at discharge

Two trials reported results for this outcome (Cao 1997; Dondorp 2005), and they found no evidence of a difference between the groups (1253 participants, 2 trials, Analysis 1.8).

### Coma recovery time

The three trials that reported median coma recovery time had inconsistent results (see Appendix 3). Frequency of measuring this outcome varied between the trials (see Appendix 2). Two trials reported mean coma recovery time (Anh 1989; Anh 1995). There was no evidence of a difference between the groups, although the data were skewed and the results were inconsistent (231 partic-

ipants, 2 trials, Analysis 1.9). One trial reported the mean, median, and mode for this outcome (Hien 1992), and the difference between these results suggest the data are skewed.

### Time to hospital discharge

Two trials reported this outcome as a median (Cao 1997; Dondorp 2005). The results were consistent and showed no evidence of a difference between the groups (see Appendix 3). One trial reported this outcome as a mean (Newton 2003) with no evidence of a difference between the groups (113 participants, 1 trial, Analysis 1.10). The data appear skewed.

### Fever clearance time

Two trials reported this outcome as a mean (Hien 1992; Anh 1995). There was no evidence of a difference between the groups, although the data appeared to be skewed and the results inconsistent (251 participants, 2 trials, Analysis 1.11). Two trials reported this outcome as a median (Cao 1997; Newton 2003), and the results were inconsistent (see Appendix 3). The frequency with which this outcome was measured differed between the trials (see Appendix 2).

### Parasite clearance time

Three trials reported parasite clearance time of 50% as a mean (Anh 1989; Hien 1992; Anh 1995). Treatment with artesunate was associated with a reduction in parasite clearance time in all three trials (MD 8.14 h, 95% CI 11.55 to 4.73; 292 participants, 3 trials, Analysis 1.12). Two trials reported median parasite clearance times of 50% (Newton 2003; Cao 1997), and the results were inconsistent (see Appendix 3). The frequency with which this outcome was measured differed between the trials (see Appendix 2).

### Adverse effects

No trial reported discontinuation of medication. With the exception of hypoglycaemia, all adverse effects reported could be attributable to malaria. Artesunate was associated with less hypoglycaemia after admission, both in the two trials that measured blood glucose routinely (RR 0.46, 95% CI 0.25 to 0.87; 185 participants, 2 trials, Analysis 1.13, subgroup 1) and in the one trial that only measured this outcome in participants with clinical signs of hypoglycaemia (RR 0.32, 95% CI 0.13 to 0.79; 1461 participants, 1 trial, Analysis 1.13, subgroup 2).

## DISCUSSION

Treatment with artesunate resulted in a significant reduction in mortality, parasite clearance time, and hypoglycaemia in people with severe malaria in Asia. There was no evidence of a difference in coma recovery time, time to hospital discharge, fever clearance time, or adverse effects other than hypoglycaemia. The number of participants with neurological sequelae is too small to draw

any conclusions from these data. Subgroup analyses showed that the beneficial effect of artesunate was most marked in preventing death after 48 hours and occurred in cerebral malaria as well as all categories of severe malaria. One trial suggests that the benefit of artesunate is even greater in people with hyperparasitaemia.

Interpretation of these results is complicated by a number of different factors. The most important of these is that all of the trials were conducted in Asia and that most of the participants were adults. The biology and epidemiology of severe malaria is different in children who tend to present with a more severe spectrum of disease. It is therefore difficult to extrapolate these findings to African children who have the highest burden of severe disease. Differing quinine sensitivity patterns in South-East Asia may mean the magnitude of the beneficial effect of artesunate may not be as great in other parts of the world.

A wide variation in trial design also complicates interpretation of these results. Subgroup analyses showed that excluding poor quality trials, trials with no loading dose of quinine, and those in which all participants had cerebral malaria did not alter the reduction in mortality. Five out of six trials administered unmatched additional oral antimalarials to the intervention and control group, introducing a possible source of confounding factors. The trials also varied in their vigilance for hypoglycaemia, an important and reversible cause of death in patients with severe malaria, and which occurred with lower frequency in the artesunate arms. This could impair the ability of trials to quantify the benefits of artesunate as an antimalarial.

Despite these comments, the beneficial effect of intravenous artesunate upon mortality was considerable, and this is a very important intervention to improve the outcome in this major disease. Intramuscular artesunate would be particularly appropriate for resource-poor settings, but there were insufficient data for this review to establish the effectiveness of this formulation compared to quinine.

## **AUTHORS' CONCLUSIONS**

## **Implications for practice**

Intravenous artesunate is the drug of choice for adults with severe malaria, particularly if acquired in Asia. This review did not identify sufficient data to make firm conclusions about the treatment of children or the effectiveness of intramuscular artesunate. This review highlights the inadequate routine measurement of blood glucose, which ideally should be checked several times a day as advocated by recent World Health Organization guidelines (WHO 2006).

## **Implications for research**

This review highlights a number of areas requiring further research. In particular, there is an urgent need to establish the comparative effectiveness of artesunate and quinine for severe malaria in African children. The ongoing study identified by this review has been designed to answer both this question as well as the relative effectiveness of intramuscular artesunate in this group. The applicability of these results to Asian children and the ethics of further research are points of debate. This review provides limited information regarding differences in hypoglycaemia and neurological sequelae between the two treatments, which impairs the ability to quantify the benefits of artesunate as an antimalarial. Both these outcomes are important in severe malaria, and future trials should include routine monitoring of blood glucose and prolonged neurological follow up for all participants.

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\* Hien TT, Arnold K, Vinh H, Cuong BM, Phu NH, Chau TT, et al. Comparison of artemisinin suppositories with intravenous artesunate and intravenous quinine in the treatment of cerebral malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1992;**86**(6):582–3.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Anh 1989

Methods	Generation of allocation sequence: random-number tables (personal communication from author) Allocation concealment: open Blinding: open label Inclusion of all randomized participants: not reported
Participants	Number: 41 enrolled Inclusion criteria: adults > 16 yr old with cerebral malaria ( <i>Plasmodium falciparum</i> parasitaemia > 1000/mm <sup>3</sup> and Glasgow Coma Scale of 14 or less not attributable to any cause other than malaria) Exclusions: not specified
Interventions	1. Artesunate: 60 mg intravenous (IV) at 0, 4, 24, and 48 h 2. Quinine: 20 mg/kg IV loading dose over 4 h at 0 h then 10 mg/kg IV every 8 h until able to swallow then 10 mg/kg by mouth every 8 h until day 7
Outcomes	1. Death 2. Coma recovery time 3. Parasite clearance time of 50% Not included in the review: 4. Parasite clearance time of 95%
Notes	Location: Vietnamese hospital Transmission: not specified Date: February to December 1989 Funding: Roche Asian Research Foundation supplied artesunate (personal communication from author) Additional antimalarials: none

#### Anh 1995

Methods	Generation of allocation sequence: central randomization (personal communication from author) Allocation concealment: sealed envelopes (personal communication from author) Blinding: open label Inclusion of all randomized participants: not reported
Participants	Number: 190 enrolled Inclusion criteria: adults 15 to 65 yr with cerebral malaria (asexual <i>Plasmodium falciparum</i> parasitaemia and clinical signs of cerebral malaria alone or associated with other visceral complications) Exclusion criteria: associated <i>P. vivax</i> parasitaemia, pregnancy, and concomitant diseases such as diabetes mellitus, stroke, meningitis, head trauma, pulmonary tuberculosis, or AIDS
Interventions	1. Artesunate: 60 mg intravenous (IV) at 0, 4, 24, and 48 h 2. Quinine: 10 mg/kg IV over 4 h at 0 h then 10 mg/kg IV every 8 h until able to swallow then quinine by mouth at similar doses every 8 h until day 7

**Anh 1995** (Continued)

Outcomes	<ol style="list-style-type: none"> <li>1. Death within 24 h</li> <li>2. Death after 24 h</li> <li>3. Coma recovery time</li> <li>4. Fever clearance time</li> <li>5. Parasite clearance time of 50%</li> </ol> <p>Not included in the review:</p> <ol style="list-style-type: none"> <li>6. Parasite clearance time of 95%</li> <li>7. Parasite clearance time of 100%</li> <li>8. Time to sit</li> <li>9. Time to take oral by self medication</li> </ol>
Notes	<p>Location: Vietnamese clinical research centre          Transmission: not specified          Date: July 1992 to May 1995          Funding: World Health Organization          Additional antimalarials: artesunate given mefloquine by mouth 15 mg/kg at day 7; quinine none</p>

**Cao 1997**

Methods	<p>Generation of allocation sequence: computer generated (personal communication from author)          Allocation concealment: sealed envelopes          Blinding: open label          Inclusion of all randomized participants: 100% (personal communication from author)</p>
Participants	<p>Number: 72 enrolled          Inclusion criteria: children &lt; 15 yr with severe malaria (asexual <i>Plasmodium falciparum</i> parasitaemia plus at least 1 of the following: coma (Blantyre Coma Scale less than or equal to 3), severe anaemia (capillary haematocrit &lt; 15%) with parasitaemia (&gt; 10,000/<math>\mu</math>L); hyperparasitaemia (&gt; 10% parasitized red blood cells or parasitaemia &gt; 500,000/<math>\mu</math>L); jaundice (obvious clinically or serum bilirubin &gt; 48 <math>\mu</math>mol/L); hypoglycaemia (blood glucose &lt; 2.2 mmol/L); spontaneous bleeding (eg gastrointestinal haemorrhage); shock (systolic blood pressure &lt; 50 mmHg if aged &lt; 6 yr, or &lt; 70 mmHg if aged 6 to 14 yr); repeated generalized convulsions (3 or more in 24 h despite cooling); renal impairment (serum creatinine &gt; 177 <math>\mu</math>mol/L, or urine output &lt; 12 mL/kg/24 h that fails to improve despite rehydration)          Exclusion criteria: severe diarrhoea, mixed infection with <i>P. vivax</i>, prior treatment with quinine &gt; 60 mg/kg, artemisinin &gt; 20 mg/kg, or artesunate &gt; 2 mg/kg during the illness episode, or any antimalarial treatment continuing for &gt; 48 h</p>
Interventions	<ol style="list-style-type: none"> <li>1. Artesunate: 3 mg/kg intramuscular (IM) at 0 h then 2 mg/kg IM at 12, 24, 48, and 72 h</li> <li>2. Quinine: 20 mg/kg intravenous (IV) loading dose over 4 h (omitted if pretreatment with quinine) then 10 mg/kg IV every 8 h up to day 7</li> <li>3. [Not relevant to review: rectal artemisinin]</li> </ol>
Outcomes	<ol style="list-style-type: none"> <li>1. Death</li> <li>2. Number survived with neurological sequelae</li> <li>3. Fever clearance time (all patients, excluding superinfections)</li> <li>4. Coma resolution</li> <li>5. Parasite clearance time of 50%</li> <li>6. Period in hospital</li> <li>7. Hypoglycaemia</li> </ol>

**Cao 1997** (Continued)

	<p>8. Adverse effects            Not included in this review:            9. Number survived well            10. Time to death from admission            11. Parasite clearance time of 90%            12. Parasite clearance time of 100%            13. Number with acute renal failure            14. Shock            15. Convulsions            16. Deterioration of coma score            17. Gastrointestinal bleeding            18. Anaemia            19. Chest infection            20. Urinary tract infection            21. Other infection            22. Reticulocyte count at admission, on day 5, at discharge            23. Haematocrit at admission, on day 5, at discharge</p>
Notes	<p>Location: Vietnamese hospital            Transmission: not specified            Date: August 1992 to March 1995            Funding: Wellcome Trust of Great Britain            Additional antimalarials given: artesunate arm received mefloquine by mouth 15 mg/kg at 96 h; quinine arm given sulfadoxine-pyrimethamine 500 mg/25 mg on day 7</p>

**Dondorp 2005**

Methods	<p>Generation of allocation sequence: computer generated            Allocation concealment: sealed envelopes            Blinding: open label; the trial centre, microscopists assessing blood slides, and data analysts were blinded            Inclusion of all randomized participants: 100%</p>
Participants	<p>Number: 1461 enrolled            Inclusion criteria: adults and children &gt; 2 yr with severe malaria (positive blood antigen stick test for <i>Plasmodium falciparum</i> and a diagnosis of severe malaria, according to the admitting physician)            Exclusion criteria: convincing history of full treatment with quinine (40 mg/kg on the first day and 30 mg/kg on any subsequent day) or an artemisinin derivative for more than 24 h before admission, known allergy to 1 of the artemisinin derivatives or quinine</p>
Interventions	<p>1. Artesunate: 2.4 mg/kg intravenous (IV) at 0, 12, and 24 h then 2.4 mg/kg IV every 24 h until able to swallow then 2 mg/kg by mouth until day 7            2. Quinine: 20 mg/kg IV loading dose then 10 mg/kg every 8 h until able to swallow then 10 mg/kg by mouth every 8 h until day 7</p>
Outcomes	<p>1. In-hospital death            2. Death within 48 h of entry            3. Death after 48 h of entry            4. In-hospital death (blood-smear positive)</p>

**Dondorp 2005** (Continued)

	<ul style="list-style-type: none"> <li>5. Neurological sequelae</li> <li>6. Time to discharge (median, intraquartile range, and range)</li> <li>7. Hypoglycaemia after entry</li> </ul> <p>Not included in the review:</p> <ul style="list-style-type: none"> <li>8. Combined outcome: in hospital death or neurological sequelae</li> <li>9. Fetal death</li> <li>10. Time to speak (median, intraquartile range, and range)</li> <li>11. Time to eat (median, intraquartile range, and range)</li> <li>12. Time to sit (median, intraquartile range, and range)</li> <li>13. Convulsions after entry</li> <li>14. Shock developing after entry</li> <li>15. Blackwater fever developing after entry</li> <li>16. Dialysis after entry</li> <li>17. Vasopressor treatment after entry</li> <li>18. Mechanical ventilation after entry</li> </ul>
Notes	<p>Location: hospitals in Bangladesh, Myanmar, India, and Indonesia</p> <p>Transmission: not specified</p> <p>Date: June 2003 to May 2005</p> <p>Funding: Wellcome Trust grant</p> <p>Additional antimalarials: both arms except in India and Bangladesh were given doxycycline (100 mg every 12 h for 7 d) once able to swallow</p>

**Hien 1992**

Methods	<p>Generation of allocation sequence: randomization tables (personal communication from author)</p> <p>Allocation concealment: sealed envelopes</p> <p>Blinding: participant blinded</p> <p>Inclusion of all randomized participants: not reported</p>
Participants	<p>Number: 61 enrolled</p> <p>Inclusion criteria: cerebral malaria (<i>Plasmodium falciparum</i> parasitaemia with clinical signs of malaria and a Glasgow Coma Scale &lt; 10)</p> <p>Exclusion criteria: not specified</p>
Interventions	<ul style="list-style-type: none"> <li>1. Artesunate: 60 mg intravenous (IV) at 0, 4, 24, and 48 h</li> <li>2. Quinine: 500 mg IV over 4 h then 500 mg IV every 8 h until able to swallow then 500 mg by mouth every 8 h until day 14</li> <li>3. [Not relevant to review: rectal artemisinin]</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>1. Fever clearance time</li> <li>2. Parasite clearance time of 50%</li> <li>3. Time to regain full consciousness</li> <li>4. Death</li> </ul> <p>Not included in the review:</p> <ul style="list-style-type: none"> <li>5. Parasite clearance time of 90%</li> <li>6. Parasite clearance time of 100%</li> </ul>

**Hien 1992** (Continued)

Notes	Location: intensive care unit in Vietnam Transmission: not specified Date: 1989 to 1990 Funding: artesunate was provided by Professor Li Guo Qiao Additional antimalarials: artesunate arm had mefloquine (by mouth 500 mg) once able to swallow
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**Newton 2003**

Methods	Generation of allocation sequence: computer generated Allocation concealment: open randomization Blinding: open label Inclusion of all randomized participants: 100%
Participants	Number: 113 enrolled, 100 analysed Inclusion criteria: adults aged 15 yr or above with severe malaria (single-species <i>Plasmodium falciparum</i> parasitaemia > 0.1% plus at least 1 of following: Glasgow Coma Scale < 11; haematocrit < 20% with asexual parasitaemia > 100,000/ $\mu$ L; total serum bilirubin > 50 $\mu$ mol/L with asexual parasitaemia > 100,000/ $\mu$ L; serum creatinine > 264 mol/ $\mu$ L with urine output < 400 mL/24 h; systolic blood pressure < 80 mmHg with cool extremities; asexual parasitaemia > 10%; plasma lactate level > 4 mmol/L; plasma glucose level < 2.2 mmol/L; plasma venous bicarbonate level < 15 mmol/L Exclusion criteria: pregnancy, contraindications to study drugs, artesunate, mefloquine, or significant quinine (> 2 g) intake in the previous 24 h
Interventions	1. Artesunate: 2.4 mg/kg intravenous (IV) at 0 h then 1.2 mg/kg at 12 h then 1.2 mg/kg every 24 h until able to swallow then 12 mg/kg by mouth every 24 h over 7 days 2. Quinine: 20 mg/kg IV over 4 h loading dose then 10 mg/kg IV every 8 until able to swallow then 10 mg/kg by mouth until day 7
Outcomes	1. Fever clearance time 2. Parasite clearance time of 50% 3. Time to regain full consciousness 4. Death 5. Hypoglycaemia 6. Adverse effects Not included in the review: 7. Parasite clearance time of 90% 8. Parasite clearance time of 100%
Notes	Location: 2 hospitals in Thailand Transmission: seasonal low intensity Date: May to July 1994 and 1995 to 2001 Funding: Wellcome Trust of Great Britain Additional antimalarials: once able to swallow some participants in both arms were given additional antimalarials, but the drug given varied during the trial; AS: no additional antimalarial (n = 22), mefloquine 15 mg/kg (n = 1), mefloquine 25 mg/kg in 2 doses (n = 22), doxycycline 100 mg every 12 h for 7 d (n = 14); quinine: no additional antimalarial (n = 20), tetracycline 250 mg every 12 h for 7 d (n = 19), doxycycline 100 mg every 12 h for 7 days (n = 15)

n: number of participants.

### Characteristics of excluded studies *[ordered by study ID]*

Awad 2003	Not a randomized controlled trial
Barnes 2004	Not severe malaria
Bounyasong 2001	Not severe malaria
Haroon 2005	A quasi-randomized controlled trial in which the first patient was allocated a treatment at random and then future patients were allocated their treatment using an alternating pattern
Krudsood 2003	Not a randomized controlled trial
Li 1990	Not severe malaria
McGready 2001a	Not severe malaria
McGready 2001b	Not a randomized controlled trial
Mohanty 2004	Not a randomized controlled trial (quasi-randomized)
Newton 2001	Treatment comparison is artesunate versus artesunate and quinine
Pukrittayakamee 2004	Not severe malaria
Win 1992	Not a randomized controlled trial
Zhao 2001	Not severe malaria

## Characteristics of ongoing studies *[ordered by study ID]*

### AQUAMAT

Trial name or title	"The AQUAMAT trial: An open label randomised comparison of injectable artesunate and quinine in children with severe falciparum malaria in Africa"
Methods	-
Participants	Inclusion criteria: OptiMal malaria rapid test positive; and treating physician considers patient to have severe malaria Exclusion criteria: patient has received more than or equal to 24 h of effective treatment with quinine or an artemisinin derivative; or patient has known allergy to quinine or an artemisinin derivative
Interventions	1. Intramuscular artesunate versus intramuscular quinine 2. Intravenous artesunate versus intravenous quinine
Outcomes	1. In-hospital mortality 2. Neurological sequelae 3. Recovery times
Starting date	18 July 2005
Contact information	Prof Nicholas White, Wellcome Unit, Faculty of Tropical Medicine, 420/6 Rajvithi Road, Bangkok, 10400, Thailand +66 23549172 +66 23549169 nickw@tropmedres.ac
Notes	ISRCTN: 50258054 Design: open, randomized, multicentre trial Location: Mozambique, Kenya, Gambia, Ghana Target recruitment number: 5300 End of recruitment date: 31 December 2005 End of follow-up date: 31 April 2009

## DATA AND ANALYSES

### Comparison 1. Artesunate vs quinine

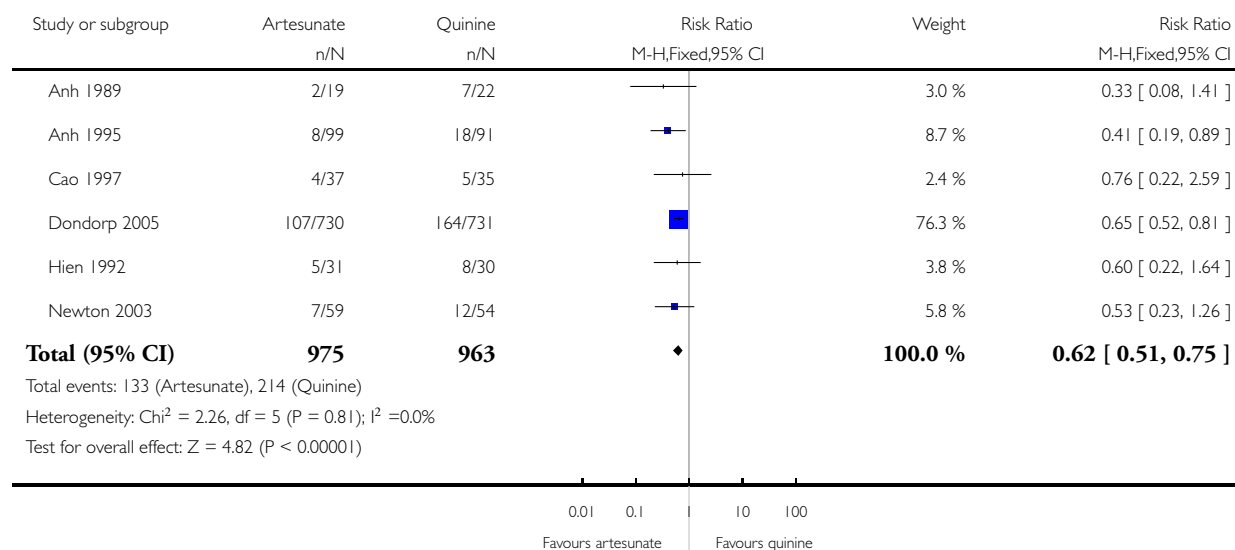
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	6	1938	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.51, 0.75]
2 Death: time since admission to hospital [subgroup analysis]	3	3292	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.52, 0.81]
2.1 Death within 48 h	3	1646	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.57, 1.05]
2.2 Death after 48 h	3	1646	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.38, 0.74]
3 Death: allocation concealment [subgroup analysis]	6	1938	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.51, 0.75]
3.1 Adequate allocation concealment	4	1784	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.51, 0.77]
3.2 Inadequate allocation concealment	2	154	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.22, 0.97]
4 Death: cerebral malaria [subgroup analysis]	6	1938	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.51, 0.75]
4.1 All participants have cerebral malaria	3	292	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.25, 0.78]
4.2 Severe malaria	3	1646	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.52, 0.80]
5 Death: loading dose vs no loading dose of quinine [subgroup analysis]	6	1938	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.51, 0.75]
5.1 No loading dose	2	251	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.25, 0.87]
5.2 Loading dose	4	1687	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.52, 0.78]
6 Death: participant age [subgroup analysis]	6	1938	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.51, 0.75]
6.1 Adults (15/16 years +)	4	405	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.29, 0.75]
6.2 Children 2 to 15 years	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.22, 2.59]
6.3 All ages	1	1461	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.52, 0.81]
7 Death: intravenous vs intramuscular artesunate [subgroup analysis]	6	1938	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.51, 0.75]
7.1 Intravenous artesunate	5	1866	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.50, 0.75]
7.2 Intramuscular artesunate	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.22, 2.59]
8 Neurological sequelae at discharge	2	1253	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [0.64, 7.63]
9 Coma recovery time	2	231	Mean Difference (IV, Random, 95% CI)	2.11 [-19.17, 23.40]
10 Time to hospital discharge	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Fever clearance time	2	251	Mean Difference (IV, Random, 95% CI)	-13.58 [-55.09, 27.92]
12 Parasite clearance time of 50%	3	292	Mean Difference (IV, Random, 95% CI)	-8.14 [-11.55, -4.73]
13 Hypoglycaemia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Routine monitoring	2	185	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.25, 0.87]
13.2 Clinical monitoring	1	1461	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.13, 0.79]

### Analysis 1.1. Comparison 1 Artesunate vs quinine, Outcome 1 Death.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 1 Death

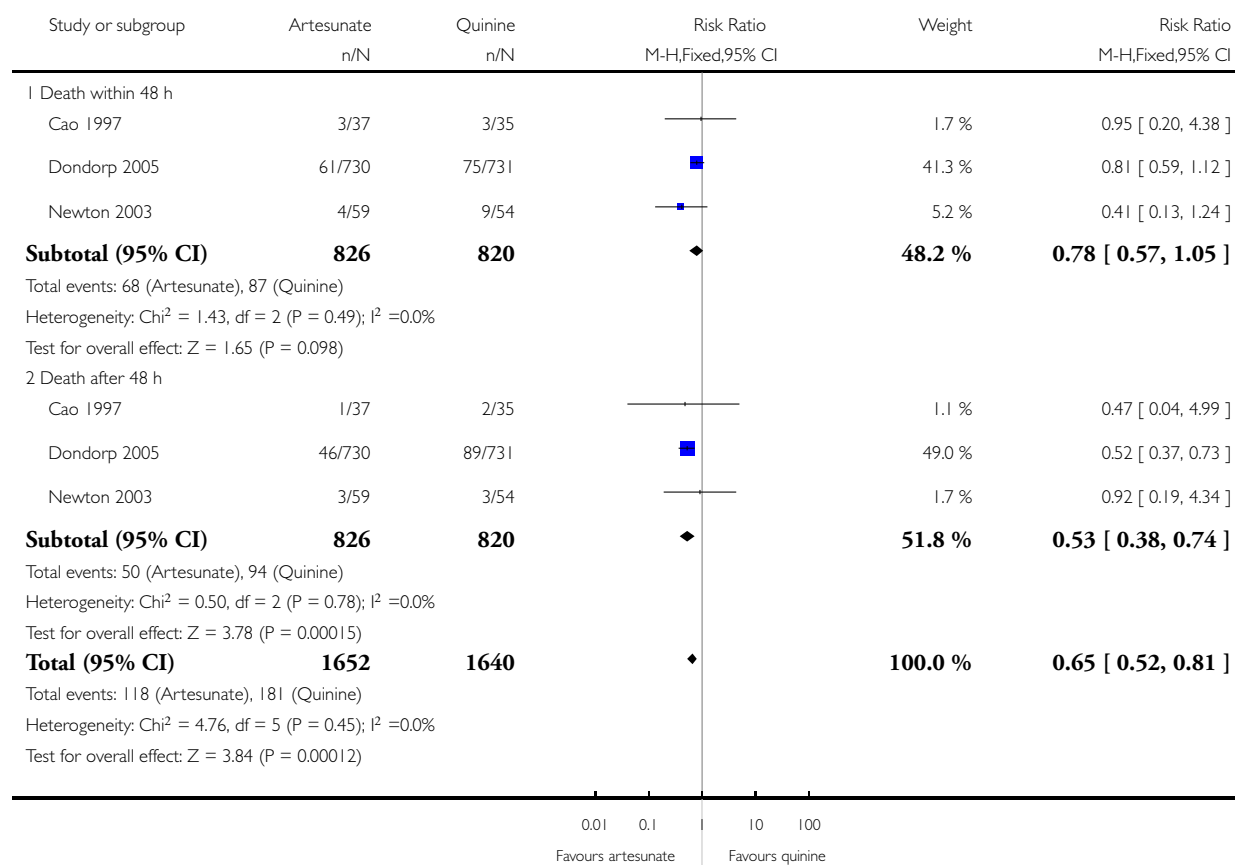


## Analysis 1.2. Comparison 1 Artesunate vs quinine, Outcome 2 Death: time since admission to hospital [subgroup analysis].

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 2 Death: time since admission to hospital [subgroup analysis]

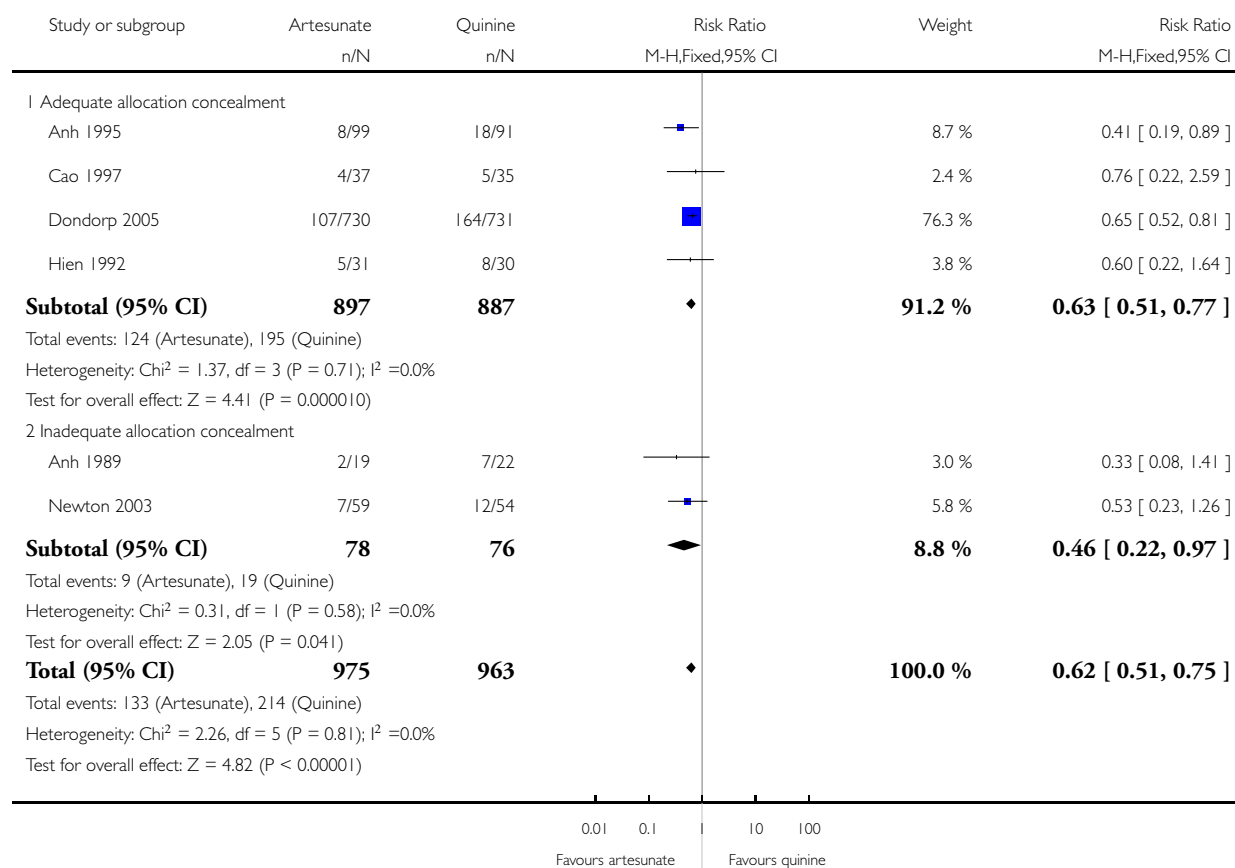


### Analysis 1.3. Comparison 1 Artesunate vs quinine, Outcome 3 Death: allocation concealment [subgroup analysis].

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 3 Death: allocation concealment [subgroup analysis]

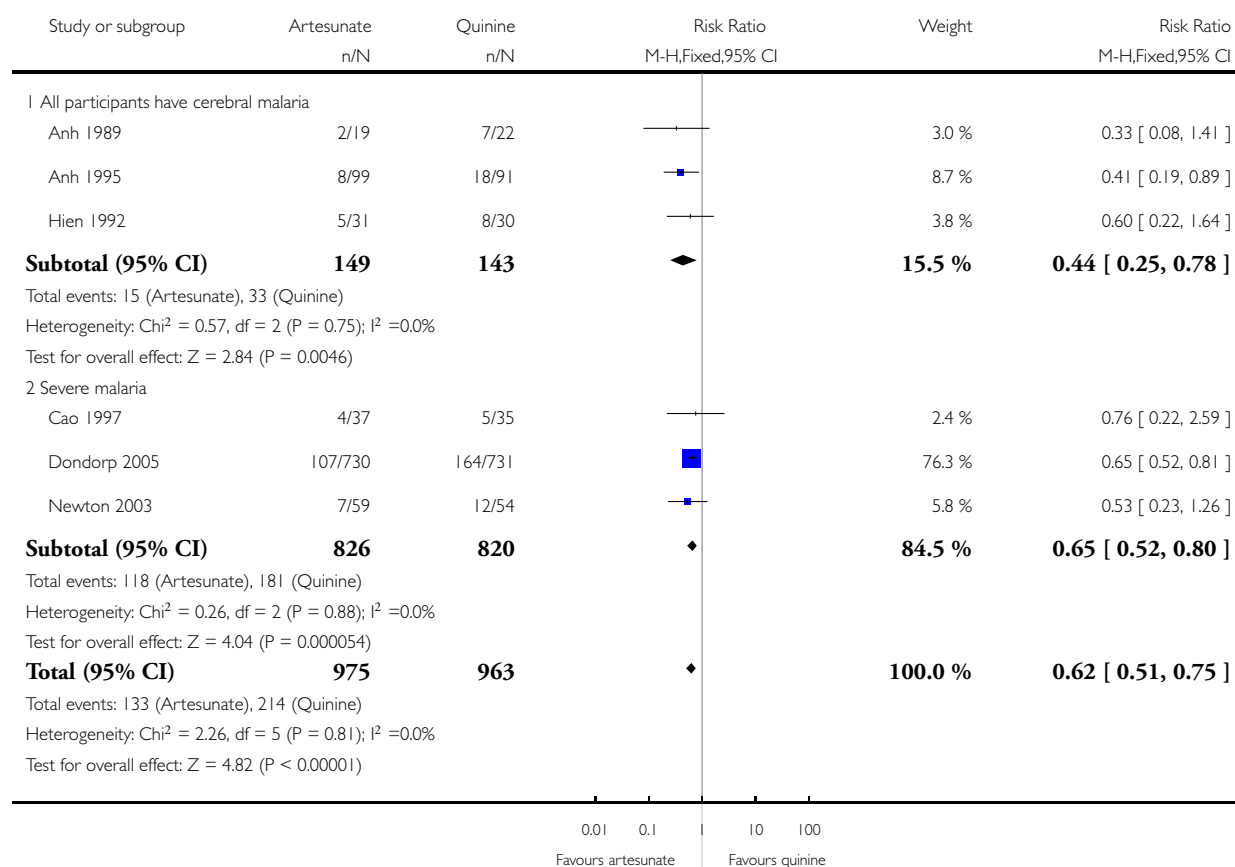


#### Analysis 1.4. Comparison 1 Artesunate vs quinine, Outcome 4 Death: cerebral malaria [subgroup analysis].

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 4 Death: cerebral malaria [subgroup analysis]

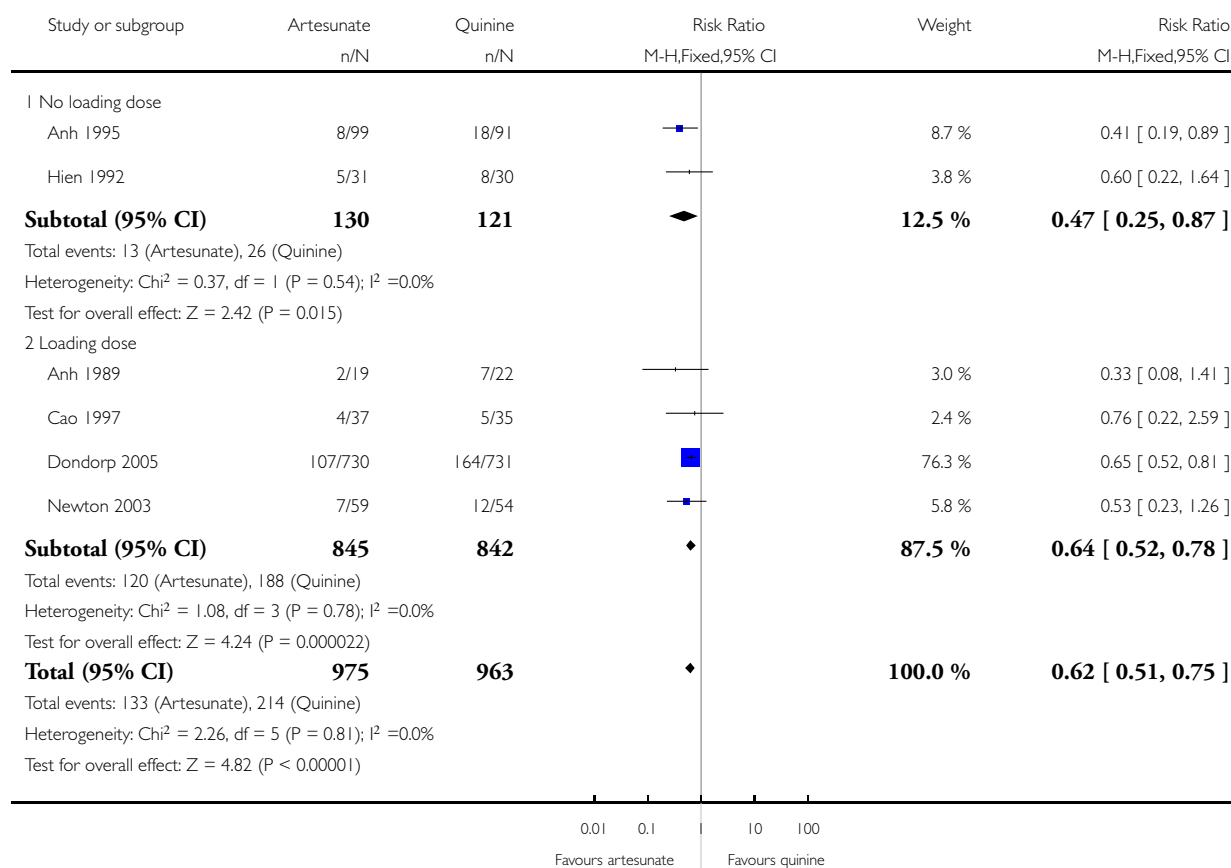


**Analysis 1.5. Comparison 1 Artesunate vs quinine, Outcome 5 Death: loading dose vs no loading dose of quinine [subgroup analysis].**

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 5 Death: loading dose vs no loading dose of quinine [subgroup analysis]

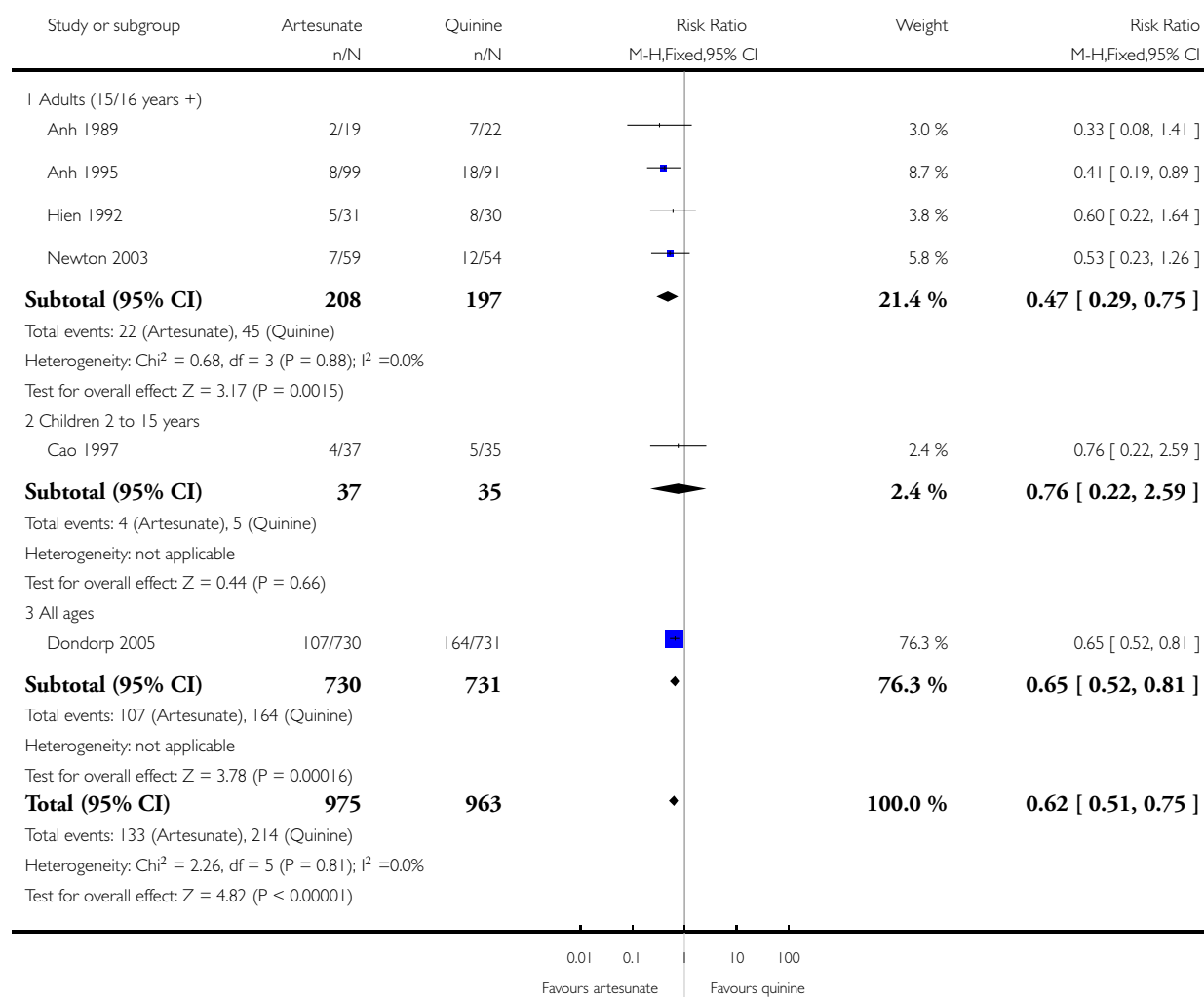


## Analysis 1.6. Comparison 1 Artesunate vs quinine, Outcome 6 Death: participant age [subgroup analysis].

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 6 Death: participant age [subgroup analysis]

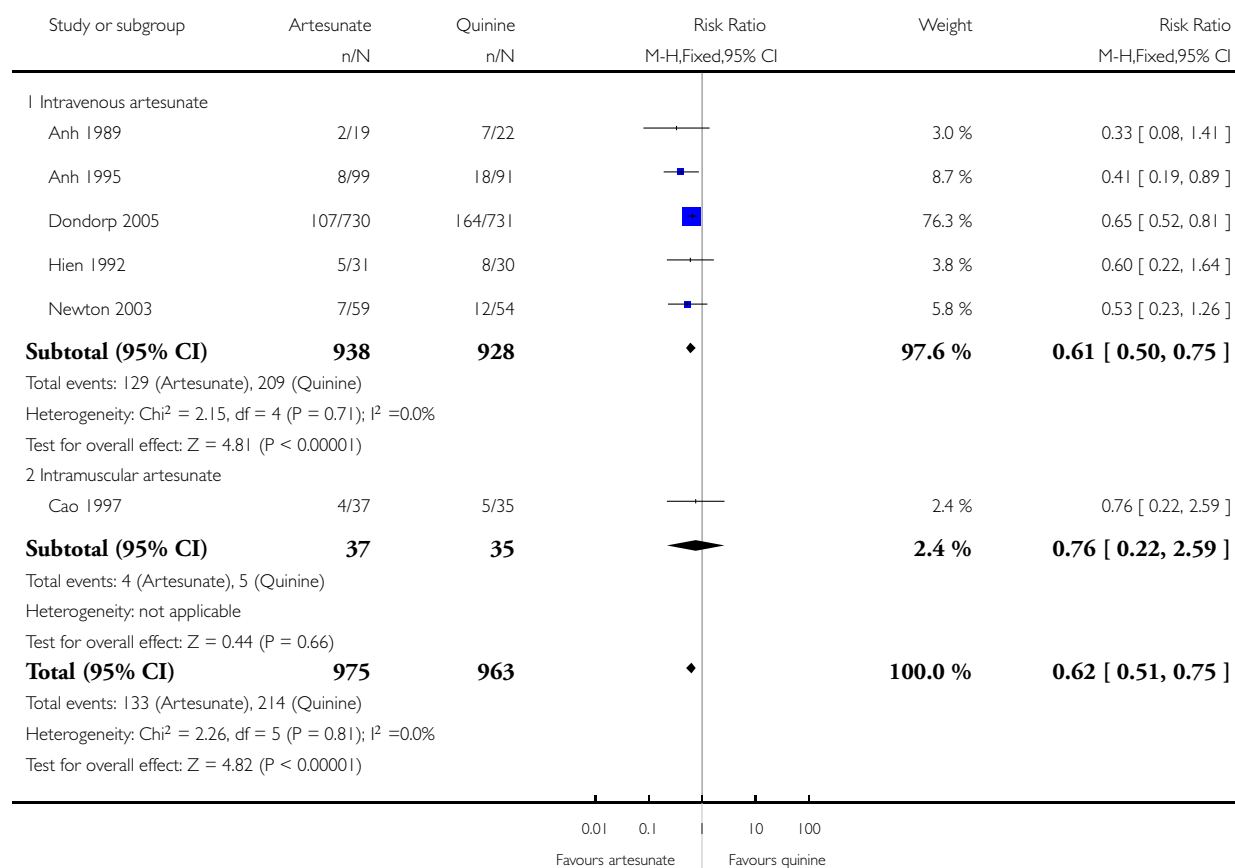


### Analysis I.7. Comparison I Artesunate vs quinine, Outcome 7 Death: intravenous vs intramuscular artesunate [subgroup analysis].

Review: Artesunate versus quinine for treating severe malaria

Comparison: I Artesunate vs quinine

Outcome: 7 Death: intravenous vs intramuscular artesunate [subgroup analysis]

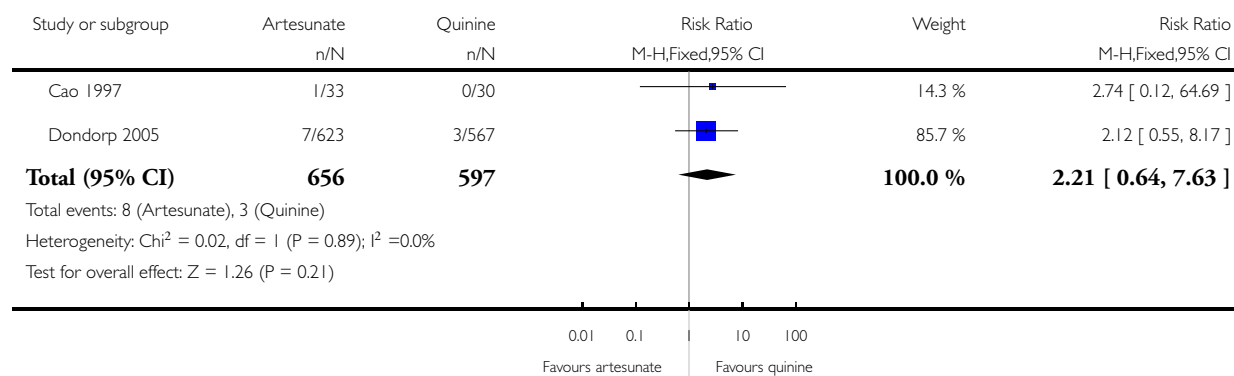


### Analysis 1.8. Comparison 1 Artesunate vs quinine, Outcome 8 Neurological sequelae at discharge.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 8 Neurological sequelae at discharge

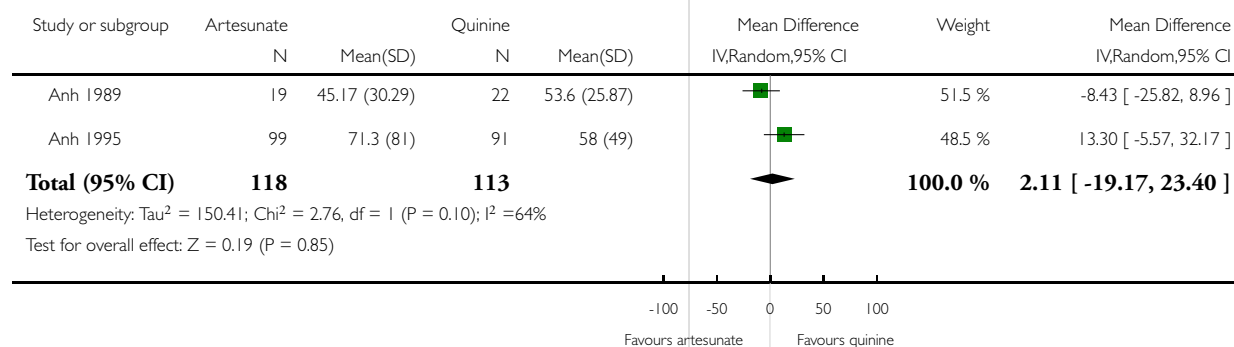


### Analysis 1.9. Comparison 1 Artesunate vs quinine, Outcome 9 Coma recovery time.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 9 Coma recovery time



### Analysis 1.10. Comparison 1 Artesunate vs quinine, Outcome 10 Time to hospital discharge.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 10 Time to hospital discharge

Study or subgroup	Artesunate		Quinine		Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)		
Newton 2003	59	5.1 (3.14)	54	5 (4.5)		0.10 [ -1.34, 1.54 ]

### Analysis 1.11. Comparison 1 Artesunate vs quinine, Outcome 11 Fever clearance time.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 11 Fever clearance time

Study or subgroup	Artesunate		Quinine		Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
	N	Mean(SD)	N	Mean(SD)			
Anh 1995	99	67.36 (41.4)	91	63.3 (46.5)		59.0 %	4.06 [ -8.50, 16.62 ]
Hien 1992	31	39 (30)	30	78 (102)		41.0 %	-39.00 [ -77.00, -1.00 ]
<b>Total (95% CI)</b>	<b>130</b>		<b>121</b>			<b>100.0 %</b>	<b>-13.58 [ -55.09, 27.92 ]</b>

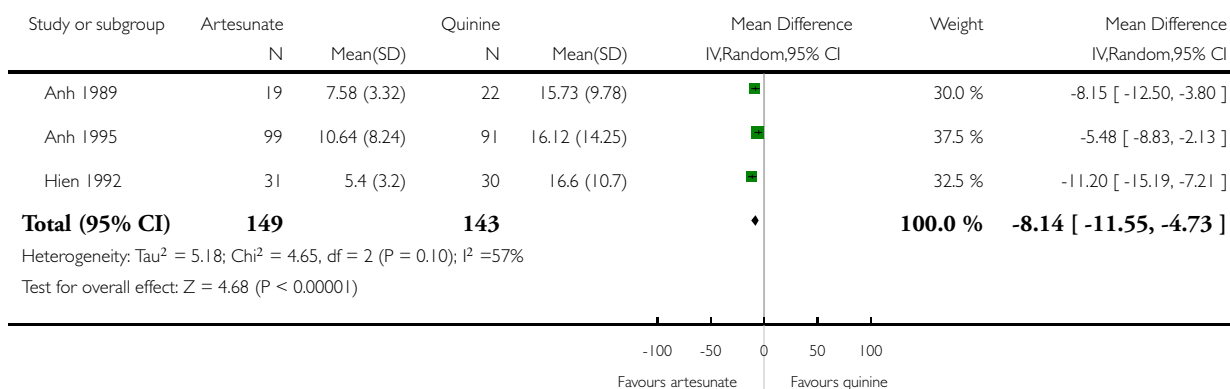
Heterogeneity:  $\tau^2 = 718.63$ ;  $\text{Chi}^2 = 4.45$ ,  $\text{df} = 1$  ( $P = 0.03$ );  $I^2 = 78\%$   
 Test for overall effect:  $Z = 0.64$  ( $P = 0.52$ )

### Analysis 1.12. Comparison 1 Artesunate vs quinine, Outcome 12 Parasite clearance time of 50%.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 12 Parasite clearance time of 50%

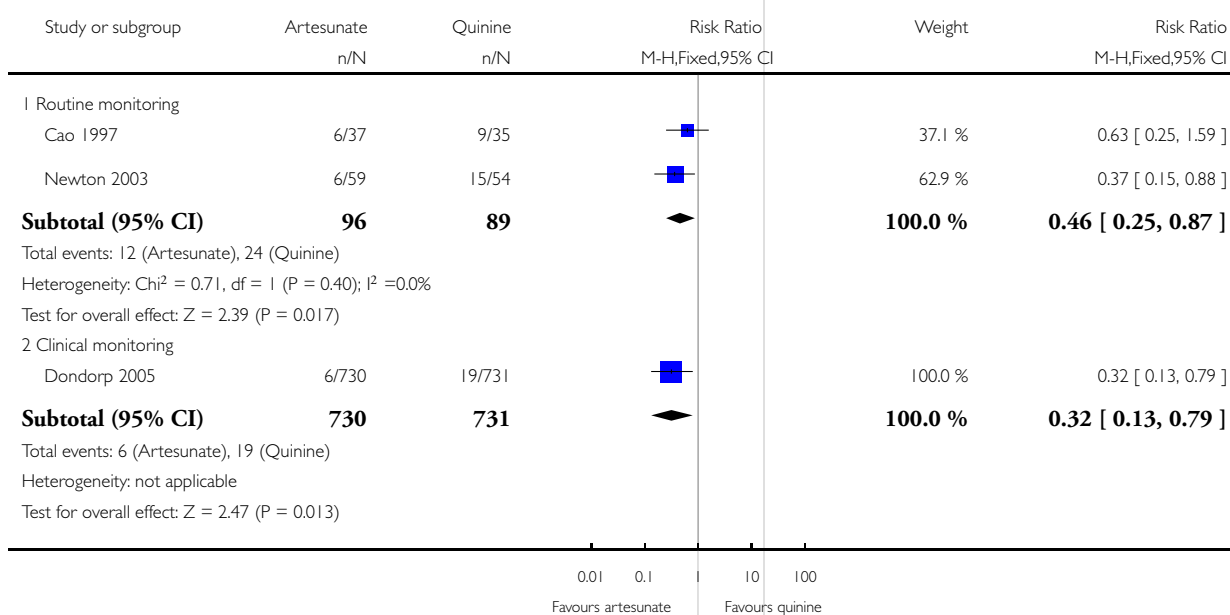


### Analysis 1.13. Comparison 1 Artesunate vs quinine, Outcome 13 Hypoglycaemia.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 13 Hypoglycaemia



## APPENDICES

### Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR <sup>a</sup>	CENTRAL	MEDLINE <sup>b</sup>	EMBASE <sup>b</sup>	LILACS <sup>b</sup>	ISI Web of Science
1	malaria	malaria	malaria	malaria	malaria	malaria
2	quinine	quinine	quinine	quinine	quinine	quinine
3	artesunate	quinimax	quinimax	quinimax	artesunate	artesunate
4	artemisinin*	CINCHONA ALKALOIDS	CINCHONA ALKALOIDS	CINCHONA-ALKALOID	artemisinin	arsumax
5	3 or 4	2 or 3 or 4	2 or 3 or 4	2 or 3 or 4	3 or 4	3 or 4
6	1 and 2 and 5	artesunate	artesunate	artesunate	1 and 2 and 5	1 and 2 and 5
7	-	arsumax	arsumax	arsumax	-	-
8	-	6 or 7	6 or 7	6 or 7	-	-
9	-	1 and 5 and 8	1 and 5 and 8	1 and 5 and 8	-	-
10	-	-	limit 9 to human	limit 9 to human	-	-

<sup>a</sup>Cochrane Infectious Diseases Group Specialized Register.

<sup>b</sup>Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration ([Higgins 2006](#)); upper case: MeSH or EMTREE heading; lower case: free text term.

### Appendix 2. Definitions of outcome measures used in the review

Trial	Death	Neurological sequelae at discharge	Coma recovery time	Time to discharge	Fever clearance time	Parasite clearance time (50%)	Hypoglycaemia	Adverse effects
<a href="#">Anh 1989</a>	Death	Not reported	Mean value (h) reported but not defined	Not reported	Not reported	Mean value (h) reported but not defined. Parasite counts every 8 h until 2 consecutive slides were negative and then ev-	Not reported	Not reported

(Continued)

						ery 24 h		
Hien 1992	Death	Not reported	Mean, median, and mode values reported in hours. Defined as time to regain full consciousness (Glasgow Coma Scale of 15/15). Glasgow Coma Scale measured at 3-h intervals until full recovery of consciousness, and at 6-h intervals thereafter	Not reported	Mean value (h) reported. Defined as time (h) until "fever clearance". The axillary temperature was measured at 3-h intervals until "fever clearance", and at 6-h intervals thereafter	Mean value (h) reported but not defined. Parasite counts performed every 4 h for 12 h, then every 6 h until 3 consecutive films were negative	Not reported	None reported
Anh 1995	Death	Not reported	Mean value (h). Defined as time until consciousness regained. Glasgow Coma Scale measured every 12 h until regained consciousness	Not reported	Mean value (h) reported but not defined. Axillary temperature was recorded every 6 h until 4 consecutive temperatures were < 37.5 °C	Mean value (h) reported but not defined. Parasite count measured every 6 h until 3 consecutive blood smears were negative	Not reported	Not reported
Cao 1997	Death	Number survived with neurological sequelae. Case definition for neurological sequelae: abnormal neurological signs	Median value (h) reported. Defined as time (h) for Blantyre Coma Score to become 5/5. Coma score assessed every 4	Median value (d) reported	Median value (h) reported. Defined as time until temperature first dropped to 37.5 °C or below and remained below this level	Median value (h) reported but not defined. Parasite count measured every 4 h (or more frequently if critically ill) for	Blood glucose < 2.2 mmol/L. Blood glucose measured every 4 h for first 24 h and then every 6 h until discharge	Acute renal failure requiring dialysis, shock, convulsions, deterioration of coma score, gastrointestinal bleeding,

(Continued)

		and/or symptoms at time of discharge from hospital that were not present before onset of the episode of malaria as reported by the child's parents. All children had a full neurological examination on admission and at discharge from hospital (personal communication from author)	h (or more frequently if critically ill) for the first 24 h, and then every 6 h until discharge		for at least 24 h. Axillary temperature measured every 4 h (or more frequently if critically ill) for the first 24 h, and then every 6 h until discharge	the first 24 h, and then every 6 h until discharge. Once 2 successive peripheral blood films had revealed no <i>P. falciparum</i> , no further blood film was made unless indicated clinically	from hospital if indicated (coma, prostration, jaundice, or > 1 complication - personal communication from author)	anaemia requiring blood transfusion, chest infection, urinary tract infection, other infections, derangement of biochemical markers
Newton 2003	Death	Not reported	Median value (h) reported. Defined as time to reach a Glasgow Coma Scale of 15 in those participants with a score < 11/15 on admission. Glasgow Coma Scale measured every 15 min for first h, at 2 h, and then every 2 h until 12 h, every 4 h from 12 to 24 h, and every 6 h from 24 h until the	Not reported	Median value (h) reported. Defined as time until the axillary temperature first dropped below 37.5 °C and remained below that level for 24 h. Axillary temperature measured every 15 min for the first h, at 2 h, and then every 2 h until 12 h, every 4 h from 12 to 24 h, and every 6 h from 24	Median value (h) reported. Defined as time to a 50% reduction in parasite density. Parasite counts were measured at 0, 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 h, and then every 6 h until 6 h after parasite clearance	Plasma glucose less than or equal to 2.2 mmol/L. Plasma glucose measured at 0, 4, 8, 12, 16, 20, and 24 h and then every 6 h	Seizures, bleeding and sepsis after admission, pulmonary oedema, oliguria, time in intensive care unit

(Continued)

			score reached 15		h until fever cleared			
<a href="#">Dondorp 2005</a>	Death	Neurological sequelae at discharge from hospital	Not reported	Median value (d) reported	Not reported	Not reported	Blood glucose < 2.2 mmol/L. Blood glucose checked in all patients on admission and then monitored on clinical indication	Not reported

### Appendix 3. Time-to-event data: medians, ranges, and modes

Outcome	Trial	Artesunate	Quinine
Coma recovery time (h): median (range), number	<a href="#">Hien 1992</a>	35 (5 to 453); mode = 17; mean = 68.9	48 (7 to 144), mode = 43; mean = 58.1
	<a href="#">Cao 1997</a>	42 (4 to 228), n = 10	31 (4 to 66), n = 2
	<a href="#">Newton 2003</a>	17 (1 to 125), n = 16	18 (1 to 188), n = 16
Time to hospital discharge (d): median (range), number	<a href="#">Cao 1997</a>	8 (5 to 20), n = 33	8 (5 to 24), n = 29
	<a href="#">Dondorp 2005</a>	5 (0 to 54), n = 623	5 (0 to 45), n = 567
Fever clearance time (until first below 37.5 °C) (h): median (range), number	<a href="#">Cao 1997</a>	4 (4 to 198), n = 35	8 (0 to 96), n = 35
	<a href="#">Newton 2003</a>	11 (1 to 83), n = 42	13 (1 to 184), n = 42
Fever clearance time (until remains below 37.5 °C for 24 h) (h): median (range), number	<a href="#">Cao 1997</a>	84 (4 to 198), n = 35	81 (0 to 246), n = 30
	<a href="#">Newton 2003</a>	41 (3 to 138), n = 32	65 (12 to 383), n = 27
Time to parasite clearance of 50% (h): median (range), number	<a href="#">Cao 1997</a>	5.7 (2.0 to 15.3), n = 35	13.2 (2.4 to 103.0), n = 32
	<a href="#">Newton 2003</a>	9.1 (0.3 to 37.2), n = 56	8.0 (0.2 to 46.0), n = 49

### WHAT'S NEW

Last assessed as up-to-date: 25 January 2007.

30 July 2009	New search has been performed	New search conducted; no new trials for inclusion. Contact person changed.
5 August 2008	Amended	Converted to new review format with minor editing.

### HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 4, 2007

## CONTRIBUTIONS OF AUTHORS

Katharine Jones and Sarah Donegan assessed the eligibility and methodological quality of trials, extracted and analysed data, and drafted the review. David Lalloo contributed to the design and writing of the review.

## DECLARATIONS OF INTEREST

Dr David Lalloo was part of the data and safety monitoring committee for the Dondorp trial. This committee is independent, does not run or gain anything from the trial, and has a main role of protecting participants.

## SOURCES OF SUPPORT

### Internal sources

- Liverpool School of Tropical Medicine, UK.
- University of Liverpool, UK.

### External sources

- Department for International Development (DFID), UK.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2007, Issue 4 (first review version): We removed the requirement for all participants to fulfil the World Health Organization's definition for severe malaria (Gilles 2000) in view of the large number of participants this would have excluded from the review as the largest included trial used a clinical case definition. We changed the intervention from "parenteral quinine" to "intravenous, intramuscular, or rectal artesunate" to clarify that trials using artesunate suppositories were included in the review. We changed "neurological sequelae" to "neurological sequelae at discharge" to clarify the follow-up period for this outcome. We added the exploration of a number of post-hoc sources of heterogeneity for mortality after noting significant variation in study design across trials. We presented data for hypoglycaemia in a forest plot rather than a table as stated in the protocol to reflect the clinical importance of this outcome.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Antimalarials [administration & dosage; \*therapeutic use]; Artemisinins [administration & dosage; \*therapeutic use]; Injections, Intramuscular; Injections, Intravenous; Malaria [\*drug therapy; mortality]; Quinine [administration & dosage; \*therapeutic use]; Randomized Controlled Trials as Topic; Sesquiterpenes [administration & dosage; \*therapeutic use]

**MeSH check words**

Adult; Child; Humans